REMARKS

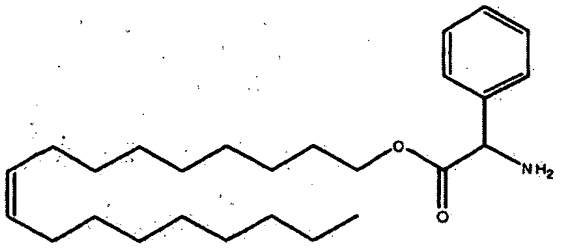
Claims 49-72 and 135-212 are pending in the subject application. In the March 18, 2009 Office Action, the Examiner withdrew claims 49-72, 135-164, 169-180 and 186-212 as allegedly drawn to non-elected subject matter. Applicants have hereinabove amended claim 184 and support for amended claim 184 may be found in the specification at, *inter alia*, page 22, line 21 - page 23, line 6, Examples 12, 13 and 15-22. Applicants maintain that no issue of new matter is raised by the amendment to claim 184. Accordingly, applicants request that the Examiner enter this Amendment. Upon entry of the Amendment, claims 165-168 and 181-185 insofar as they read on the elected species will be pending and under examination in the subject application.

Election/Restrictions

In the March 18, 2009 Office Action, the Examiner acknowledged applicants' election with traverse of Group VII, claims 165-185. However, the Examiner did not find applicants' grounds for traversal persuasive.

The Examiner alleged that the inventions in Groups I-IX are not so linked as to form a general inventive concept and they also do not share a common special technical feature. According to the Examiner, the core technical feature is the O-CO moiety because this is the only non-variable core that is common to all compounds of formula I, and this core technical feature is not a special technical feature because it fails to define a contribution over the art.

The Examiner further contended that the elected species:



α-amino-α-phenyl acetic acid octadec-(Z)-9-enyl ester

does not make a contribution over the prior art and, thus, appears not be allowable. Therefore, the Markush claim shall be rejected and claims to the non-elected inventions are held withdrawn. The Examiner determined that the entire scope claimed is not patentable.

Applicants' Response

As discussed below in applicants' response to Examiner's obviousness rejection, the elected species is patentable in view of the prior art. Applicants therefore disagree with the Examiner's statement and are of the opinion that the elected species is allowable and the entire scope of the Markush claim is allowable as well.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claim 184 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleged that claim 184, which is directed to a pharmaceutical composition for the treatment of inflammation, contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

According to the Examiner, in view of the high unpredictability of the claimed subject matter, the level of the skill in the art, and insufficient disclosure and working examples in the specification, a skilled person would not be able to carry out the invention without undue experimentation. According to the Examiner, the specification fails to provide sufficient support of the broad use of the compounds for treatment or prevention of the various inflammatory diseases that exist, necessitating one of skill in the art to perform an exhaustive search for which disease can be treated or prevented by what compounds defined in the present claims in order to practice the claimed invention.

The Examiner states that "[f]or a compound or genus to be effective against inflammation generally is contrary to medical science … Accordingly, treatments for inflammation can normally be tailored to the particular type of inflammation present, as there can be no 'magic bullet' against inflammation generally."

Applicants' Response

In response, without conceding the correctness of the Examiner's rejection, claim 184 has been amended hereinabove to clarify the claimed subject matter. As amended, claim 184 specifically provides that the pharmaceutical composition is for the treatment of an immunologically mediated acute or chronic inflammatory disease, disorder or condition. Such treatment is fully enabled by the subject specification, and exemplified by well established *in vivo* models that reliably serve the purpose of assessing the anti-inflammatory effects of the compounds of the invention in acute and chronic

autoimmune disease and immune-mediated inflammation in general including cell-mediated autoimmune reactions. Specifically:

(i) Inhibition of on adjuvant arthritis (AA) by the compounds of the invention acting as active agents per se or as adjuvants is described in an enabling manner in the specification and supported by Examples 12, 16, and 19.

AA is one of the models used according to the invention for testing the anti-inflammatory activity of the agents. AA is an experimental disease of the joints inducible in some strains of rats by immunizing with *Mycobacterium tuberculosis* in complete Freund's adjuvant (CFA). These animals develop an arthritis whose features are similar to those of rheumatoid arthritis in humans and thus serve as animal models of human arthritic conditions such as rheumatoid arthritis, reactive arthritis in Reiter's syndrome, ankylosing spondylitis and other inflammations of the joints, which appear to be mediated by the immune system. Adjuvant arthritis also serves as a model of immune-mediated inflammation in general including cell-mediated autoimmune reactions, graft rejection and allergic reaction. For example, treatments which can suppress rheumatoid arthritis include immunosuppressive agents such as corticosteroids, cyclosporin A, azathioprine, and other immunosuppressive agents which are broadly used in the treatment of autoimmune diseases. Therefore, suppression of adjuvant arthritis by a therapeutic agent indicates that the agent is potentially useful as a broad anti-inflammatory agent (see page 22, line 21-page 23, line 6 of the description).

(ii) Anti-inflammatory effects of the compounds of the invention in experimental autoimmune encephalomyelitis (EAE),

wherein the compound acts as active agents per se or as adjuvants is described in an enabling manner in the specification and supported by Examples 13, 15, and 20-22.

EAE is an experimental autoimmune disease inducible in some strains of rats by immunization with myelin basic protein (MBP) in complete Freund's adjuvant (CFA) (in Lewis rats) or with an emulsion of the rat's spinal cord in incomplete Freund's adjuvant (IFA) (in DA rats). The animal experimental disease serves as a model for the human autoimmune disease multiple sclerosis. The disease develops in the animal about 12 days after immunization and is characterized by paralysis of various degrees due to inflammation of the central nervous system (see page 38, line 24-page 39, line 3). In some strains, like the Lewis rat, the paralysis can last up to 6-7 days and the rats usually recover unless they die during the peak of their acute paralysis. In fact, EAE induced in Lewis rats is considered as a model of acute inflammation in the brain. Anti-inflammatory effects of compounds 1, 3 and 9 in EAE induced in Lewis rats are exemplified in Examples 15, 20 and 21, respectively.

In other strains of rats like the DA rat, the paralysis can be chronic and remitting. EAE in DA rats is considered as a model of chronic EAE. Within two to three weeks the animals develop cellular infiltration of the myelin sheaths of the central nervous system resulting in demyelination and paralysis. Most of the animals die, but others have milder symptoms, and some animals develop a chronic form of the disease that resembles chronic relapsing and remitting multiple sclerosis (MS) in humans. Animals with chronic EAE serve also as a model for other inflammatory diseases of the nervous system. Anti-

inflammatory effects of compounds 1 and 9 in chronic EAE induced in DA rats are exemplified in Examples 13 and 21, respectively.

(iii) Inhibition of delayed-type hypersensitivity (DTH) skin reaction by the compounds of the invention acting as active agents per se is in an enabling manner in the specification and supported by described in Examples 17 and 18.

DTH, a localized inflammatory reaction induced by cytokines (IL-3, IL-1, GM-CSF, IFN-γ, TNF-α, TNF-β) secreted by certain T_H cells when they encounter certain types of antigens, is an established experimental model for skin inflammation (see page 42, lines 5-7, in the description). The reaction is characterized by large influxes of nonspecific inflammatory cells, in which the macrophage is a major participant.

DTH can be induced in human and animals in various tissues. DTH induced in the skin of animal is an established model for acute and chronic skin inflammation manifested by various symptoms of inflammatory skin diseases and disorders known in human pathology. Several skin sensitizers, functioning as antigens, have been utilized for skin DTH induction, including trinitrochlorobenzene (TNCB), dinitrofluorobenzene, and oxazolone (as in Examples 17, 18 of the present invention). The ease of application, measurement of response (e.g. ear swelling), sampling and accessibility of draining lymph nodes has made this reaction a useful model to study immunologically driven inflammation of the skin, such as psoriasis and pemphigus vulgaris.

The animal model for DTH used according to the present

invention display similar location and type of inflammatory cells infiltrating the skin as those seen in psoriatic lesions. The swollen ear of the tested animal exhibits similar increased expression of MHC II, infiltration of the dermis with neutrophils and monocytes, and changes in the cytokine expression patterns that present essentially similar trends as the changes in cytokine expression pattern reported in the skin of human patients with psoriasis. These changes include, in particular, the changes in TNF-α and IFN-γ, IL-1, IL-2 and GM-CSF. Further related changes include increased expression of cell-adhesion molecules. Anti-inflammatory effects of Compounds 3, 5, 9 and 11 are exemplified in Examples 17 and 18.

Thus, contrary to the Examiner's assertion, the specification teaches how to assess the anti-inflammatory effects of the compounds of the invention and provides sufficient support of the broad use of the compounds for treatment or prevention of immunologically-mediated inflammatory diseases. Therefore, a skilled person would be able to carry out the invention, without undue experimentation.

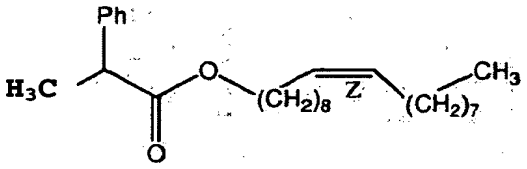
In view of the amendment to claim 184 and the preceding remarks, applicants respectfully request the Examiner reconsider and withdraw the rejection of claim 184 under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 165-168 and 181-185 under 35 U.S.C. §103(a) as allegedly obvious over Hercelin et al. (FR Patent No. 2383662) in view of Patani et al., [Patani, George

A. Bioisosterism: A rational approach in drug design. Chem. Rev. 96(1996):3147-3176].

The Examiner alleged that Hercelin et al teaches the compound:



which is a bioisostere of the presently elected compound, differing from the instantly examined species only by having a terminal methyl group instead of amino.

The Examiner also alleged that Patani et al teaches that "bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents", and that the concept of bioisosterism is "intuitive". The Examiner further alleged that bioisosteric substitutions are well-known in the art, and referred to Table 2 and Table 12 in Patani et al, allegedly showing that NH_2 and CH_3 are isosteric.

The Examiner, relying on MPEP 2144.08 II A.4(c) stated that "motivation to make the instantly examined species derives from the expectation that structurally similar compounds would possess similar biological activity, and to produce a more clinically effective agent as disclosed in Patani et al. Thus, it would have had *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to be motivated to combine the compound taught by Hercelin et al, with the disclosure on known bioisosteres from Patani et al, to interchange the secondary amino group for a methyl group in

order to produce a more clinically effective agent with a reasonable expectation of success."

Applicants' Response

Hercelin et al (FR 2383662)

Hercelin et al. discloses an ester of oleic alcohol as the active agent in a cosmetic composition useful for the treatment of local bacterial infection caused by Corynebacterium Acne. The Corynebacterium Acne bacteria release enzymes, particularly lipases and proteases capable of hydrolyzing triglyceride of the sebum into fatty acids and triglycerides, which act as irritating factors, and lead to unaesthetic cutaneous reactions manifested in the formation of different clinical types of acne, that vary from papules, pustules, cysts and comedones.

Hercelin et al. deal with the problem of unaesthetic cutaneous reactions by directly inhibiting the enzymes secreted by the bacteria, based on the findings that certain esters of oleyl alcohol have inhibiting properties on Corynebacterium Acne enzymes.

An infection by a pathogen may be treated in two completely different and unrelated routes, termed herein the "exogenous route" and the "endogenous route". The exogenous route involves an external treatment, namely applying exogenous agents that neutralize the pathogen. The endogenous route concerns the immune system of the host and involves an inflammation reaction. Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective

attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue.

Inflammation is not a synonym for infection. Even in cases where inflammation is caused by infection, the two are not synonymous: infection is caused by an exogenous pathogen, while inflammation is the response of the organism to the pathogen. In the absence of inflammation, wounds and infections would never heal and progressive destruction of the tissue would compromise the survival of the organism. It is for that reason that inflammation is normally closely regulated by the body.

Hercelin et al. relates to the treatment of bacterial infection via the exogenous route using exogenous anti-bacterial agents. A skilled person knowing the profound differences between the exogenous antibacterial treatment disclosed in Hercelin et al. and an inflammatory reaction, would certainly not be motivated to choose the compound disclosed in Hercelin et al. as an anti-inflammatory agent. Moreover, the skilled person knowing that inflammation is a positive reaction of the host against pathogen infection would not even consider inhibiting the inflammatory process and thereby interfere with the attempts of the host to protect itself. Thus, the teaching of Hercelin et al. is not at all relevant to the inventive step of the amended claims.

Patani et al

Patani et al. reviews the concept of isosterism and discloses some bioisosteric replacements, which have been used to advance drug development up until 1996. According to the

concept of isosterism, CH_3 and NH_2 are considered isosteres. But the question is: does isosterism inevitably leads to bioisosterism? Patani et al. states on page 3148, second column, last full paragraph (emphasis added):

> "Bioisosteres as initially defined by Friedman, were to include all atoms and molecules which fit the broadest definition for isosteres and *have a similar type of biological activity, which may even be antagonistic...The critical component for bioisosterism is that bioisosteres affect the same pharmacological target as agonists or antagonists* and thereby, have biological properties which are related to each other".

The compound of Hercelin et al. and the presently elected species α-amino-α-phenyl acetic acid octadec-(Z)-9-enyl ester may be considered as isosteres, but the question of whether these isosteres are also bioisosteres should be addressed by examining their biological affect on the particular lipase or protease secreted by Corynebacterium Acnes. It would be contrary to the principles of bioisosterism and senseless to state that two isosteres are bioisosteres when the activity of one is assessed in a bacterial system and that of the other is assessed in the immune system, which represent two pharmacological targets completely different and totally unrelated to each other. Therefore, the combined teaching of Hercelin et al. and Patani et al does not render the claims of the present application obvious.

The record fails to support the Examiner's assertion that the prior art compound and the elected species are

bioisosteres with regard to the Corynebacterium Acnes enzymes. Moreover, the bacterial pharmacological target is completely irrelevant to targets of the immune system. Therefore, the combined teaching of Hercelin et al. and Patani et al. does not render the claims of the present application obvious.

Patani et al. is further not relevant to the non-obviousness of the present claims for the following reason: it is stated therein that the ability of a group of bioisosteres to elicit similar biological activity has been attributed to common physiological properties such as electronegativity, steric size and lipophilicity (see page 3148, first paragraph of the left column). Thus, differences in e.g. lipophilicity or size may result in alteration of the biological activity of isosteres. NH_2 and CH_3 may have very close van der Waal's radii, but they differ a little in their electronegativity and more in their lipophilicity, and this might result in bioisosteres which present e.g., antagonistic activities.

See for example Table 12 on page 3153, right column of Patani et al. that lists the relative potencies of a group of bioisosteres which act as inhibitors of thymidylate synthase. These bioisosteres are derived form compound 20 in which hydrogen at position 9 was replaced by CH_3 or NH_2. As seen, the IC_{50} obtained for replacement with NH_2 was three-fold higher than replacement with CH_3, which means, in this case, that replacement with NH_2 resulted in a <u>less active</u> compound. Patani attributes the difference in the inhibitory activity to the differences in size and lipophilicity. In another example (see Table 13, page 3153), the replacement of methyl with the less lipophilic amino group resulted in a more

antagonistic activity of the compound. The conclusion drawn form these and other examples disclosed in Patani et al is that even when isosteres are evaluated on the same pharmacological target and behave as bioisosteres, i.e., present a similar type of biological activity, replacing, e.g., methyl with amino does not necessarily result in an improved pharmacological effect.

Obvious to try versus obvious to succeed

As discussed *supra*, the teaching of Hercelin et al. is not relevant to the present application. Further, according Patani et al., taking the approach of improving a drug candidate by synthesizing its bioisostere does not necessarily result in improved biological or pharmacological activity of the bioisostere. Thus, even if it was intuitive to try to modify a compound in order to achieve improvement, it is certainly not obvious that one would succeed based the teachings in the prior art, i.e. there is no expectation of success. Therefore, *a prima facie* case of obviousness cannot be established in the present case, and "obvious to try" is not a proper theory of obviousness in the present situation.

Applicants refer to *KSR International v. Teleflex Inc.*, 550 US 398, 82 USPQ2d 1385 (2007) ("KSR") in which the Court at 1741 cited with approval the following passage from *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006):

> "Rejections on obviousness grounds cannot be sustained by mere conclusary statements; instead, there must be some articulated reasoning with rational underpinning to support the legal conclusion

of obviousness."

Here, the Examiner stated that it would be "intuitive" to improve the compound of the prior art based on the common knowledge of bioisosterism, but failed to present any rational underpinning, which is necessary to support the legal conclusion of obviousness according to the Court in KSR. Indeed, the Court in KSR stated that fact finders may take recourse to common sense. However, here, common sense would dictate quite the opposite of what the Examiner is suggesting, particularly in light of the known principles of bioisosterism.

With regard to the issue whether everything that would be obvious to try would be obvious in the sense of 35 U.S.C. 103, KSR indicates that the "obvious to try" standard only applies when there are a finite number of identified, predictable solutions. Note KSR's analysis of obvious to try where it states, 82 USPQ2d at 1390:

> "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp."

The Federal Circuit in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1452 (Fed Cir. 2008), cited this portion of KSR, and stated at 1456-1457 that:

> "[t]he Supreme Court's analysis in KSR thus relies on several assumptions about the prior art

> landscape. First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound...Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions,"... *prima facie* case of obviousness this court further explained that this "easily traversed, small and finite number of alternatives...might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

Thus, the KSR approach based on a finite number of identified predictable solutions fails to support the obviousness reasoning by the Examiner in this case. In the present case there are not a finite number of identified predictable solutions to address the present problem, and this necessitates one to establish that there is a reasonable expectation of success in order to establish a *prima facie* case of obviousness.

Although the need to find better ways to treat immunologically-mediated inflammation may present a situation where there is pressure to solve a problem, the problem does not have a finite number of identified predictable solutions. Designing of new and improved drugs for the treatment of immunologically-mediated inflammation based on bioisosterism as suggested by the Examiner is not a predictable solution since the chemical art is highly unpredictable, as the Examiner herself acknowledged on page 6 of the Office Action.

In view of the preceding remarks, applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 165-168 and 181-185 under 35 U.S.C. §103(a).